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Antigen-specific therapies in MS — Current concepts and novel approaches

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ABSTRACT

Induction of antigen-specific tolerance is a promising therapeutic approach for autoimmune diseases. Despite many successes in animal models, translation to the clinic has been hampered by lack of efficacy, disease exacerbation and hypersensitivity reactions. Novel approaches aim at inducing tolerance to several immunodominant antigens at the same time. Besides several key issues like the route of administration, dose of antigen and nature of antigen, antigen-specific therapies should be performed early in the disease course in order to block the diversification of autoreactive specificities and thereby prevent disease progression. It is essential that clinical trials are accompanied by appropriate immunologic analyses to be used either as a parameter to monitor safety and efficacy, but also to get a better understanding of the mechanisms of disease and the respective treatment approach. Here we will discuss the mechanisms of tolerance, the experience with trials in MS and present novel approaches.

1. Introduction

Re-establishing tolerance of the immune system to autoantigens has been a longstanding goal in autoimmune research for basic and clinical immunologists. It offers the opportunity to attenuate specifically the pathogenic autoimmune response in an effective way with few side effects. Since such approaches are thought to redirect pathologic immune responses in a very specific way and correct the causes of autoimmune diseases at their roots, the induction of antigen-specific tolerance has always been considered the "holy grail" of immune therapy. Although successful in various animal models of autoimmune diseases, translation to human disease has not been successful yet.

Particularly in a chronic disease as MS, therapy should aim to specifically delete or functionally inhibit pathogenic autoreactive cells without altering the "normal" immune system. This is of importance because global immunomodulation and/or immunosuppression not only compromise immune protection but also inhibit potentially beneficial regulatory cells and autoreactive immune cells that might serve protective functions [1,2]. Thus, the ideal treatment would be early intervention using an antigen-specific tolerance protocol that selectively targets both activated and naïve autoreactive immune cells specific for multiple pathogenic epitopes that perpetuate the disease.

Over 15–20 years multiple sclerosis (MS) patients face a high risk of accruing substantial disability due to autoimmune inflammation of the brain and spinal cord. Although the etiology of MS is largely unknown, it is well accepted that the damage of the central nervous system (CNS) results from an autoimmune attack against autoantigens within the CNS, predominantly the myelin sheath [3]. Current therapies for MS inhibit the autoimmune response in a non-specific manner, are only moderately effective and can have significant side effects.

Although it is clear that several cellular and humoral components of the immune system are important in the immunopathogenesis of MS, current evidence suggests CD4+ T cells as a central factor in orchestrating the autoimmune pathogenesis of MS [4]. Autoreactive myelin-specific CD4+ T cells can also be detected in peripheral blood of healthy individuals, showing that autoreactive T cells are part of the normal T cell repertoire and that negative selection in the thymus might not be that stringent [5]. Thus peripheral mechanisms tightly controlling the activation of potentially autoreactive T cells are crucial to protect from autoimmune disease. Due to their pathogenic involvement CD4+ T cells are one logical target for therapeutic interventions. Most antigen-specific approaches used in MS so far aimed at tolerizing autoreactive T cells present in the peripheral immune system. In recent years there has been growing interest in CD8+ T cells as possible effectors in the pathogenesis of MS [6,7], The effect of antigen-specific therapies on this T cell subset has not been analyzed in detail, yet, but future studies should aim at identifying the prospects of a tolerizing strategy on CD8+ T cells.

2. Antigen-specific therapies — principles and mechanisms of tolerance

Most strategies of antigen-specific tolerance interfere at the level of antigen presentation and activation of effector T cells by antigen presenting cells (APC). In this context they can modulate T cell activation either through direct interaction with the trimolecular complex (TCR/Ag/HLA) or via regulatory mechanisms through the

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Table 1
Mechanisms of antigen-specific tolerance

Mechanism	Definition	Principle	Strategy
Clonal deletion	Apoptotic cell death of antigen-specific T cells	Administration of antigen induces apoptosis of activated T cells through cell surface receptors (eg FasL, CTLA4, PD1) or activation-induced cell death by a strong signal to the TCR	Soluble peptide or protein via mucosal, iv or sc route at high dose
Anergy	Unresponsiveness of antigen-specific T cells that is maintained even when the antigen is presented by a fully competent APC	Engagement of the trimolecular complex (TCR/Ag/HLA) without costimulatory signal provided by the APC, can be overcome by high dose IL-2	High dose mucosal or systemic antigen; APL; antigen-coupled cells
Immune deviation	Shift in immune response of T cells from a "pro-inflammatory" Th1 type to a more "protective" Th2 type of response	T cells are induced to secrete cytokines (IL-4, IL-10, TGFß) that counteract TH1 driven autoimmunity	Low dose mucosal antigen, APL
Regulatory cells	Subsets of T cells with the ability to down-regulate an immune response	Regulatory cells secrete anti-inflammatory cytokines with bystander suppression on APC and T cells and compete with effector T cells for antigen presentation	Oral tolerance, APL, TCR vaccination

induction of cytokines and regulatory cells. The basic tolerizing mechanisms include anergy, clonal deletion, immune deviation and induction of regulatory cells (Table 1). The activation of a T cell by an APC requires the interaction of the TCR with the peptide/HLA complex (signal 1) and an additional costimulatory signal (signal 2) provided by several accessory cell surface molecules. Engagement of the trimolecular complex without costimulatory signal leads to anergy, which refers to the inability of T cells to respond to the specific antigen even when it is later presented by a fully competent APC. However the costimulatory pathway can also involve negative signal to T cells by specific cell surface receptors on T cells (eg CTLA4/CD80 or CD86, PD1/PD1L). Engagement of this signaling pathway may lead to clonal deletion through apoptosis of T cells. Binding of a peptide to the TCR of activated T cells may induce activation-induced cell death (AICD) through a strong signal to the TCR.

After activation, naïve CD4+ T helper cells are skewed toward a specific effector subset expressing different cytokine patterns. While Th1 and Th17 effector T cells are considered relevant for the pathogenic immune response in autoimmune disease, it has been suggested that development of a Th2 effector T cell will counteract autoimmunity by promoting anti-inflammatory cytokines. The induction of regulatory cell type is a further mechanism used by the peripheral immune system to control autoimmunity. The mechanisms of immune tolerance are schematically depicted in Table 1.

3. Previous tolerization trials

Despite many successes of antigen-specific therapies in animals, so far the attempts in humans resulted in several difficulties including lack of efficacy, disease exacerbation and hypersensitivity reactions. Most trials until now in MS focused on MBP as target antigen but involved different routes of administration, different dosages and different nature of the antigen. The applied strategies used oral or iv administration of whole MBP, MBP peptides or a solubilized complex composed of HLA DR2 with MBP84-102, iv administration of an altered peptide ligand (APL) of MBP83-99, T cell and TCR vaccination and intramuscular injection of a DNA vaccine [8] (Table 2).

Oral tolerance is an attractive approach for the clinic particularly due to its easy route of administration and its favorable safety profile. Oral tolerance has been shown to induce clonal anergy or deletion when given at a high dose whereas low dose treatment leads to bystander suppression through the release of suppressive cytokines, such as TGF-ß, IL-4 or IL-10 by regulatory T cells. After encouraging results in animals and clinical phase I/II trials, a large phase III placebo controlled trial with oral bovine MBP failed [9]. However, an unusual large placebo effect was observed which posed difficulties in the interpretation of the data and there the discussion is still ongoing as to whether different dosage or formulation of myelin might have influenced efficacy of the treatment.

Intravenous administration of peptides at high doses can provoke AICD on previously activated T cells through a strong signal to the TCR. In two small trials in progressive MS patients the iv injection of soluble MBP peptides was well tolerated and showed favorable effect on disease progression in HLA DR2-positive patients [10,11]. Based on these results a phase III trial assessing the effect of iv injection of soluble MBP peptide is under way. However, since the mechanism of tolerance was not assessed by mechanistic studies and the activation status of MBP specific T cells in these patients is not known, we cannot definitely conclude whether AICD was induced or whether a different mechanism of tolerance is involved.

Intravenous injection of a solubilized MHC-peptide complex was used in another approach to induce antigen-specific tolerance The underlying concept is to engage the TCR of autoreactive T cells without delivering costimulatory signals, thereby inducing clonal anergy.

Table 2
Overview of current antigen-specific therapies tested in MS

Antigen-specific therapy	Treatment	Disease course	Trial design	Clinical and MRI outcome	Impact on immune response in MS	Further trial planned/ ongoing
DNA vaccine (BHT-3009)	Plasmid encoding full length human MBP	RR, SP	Randomized double blind placebo controlled trial	Safe, well tolerated, favourable on MRI	Down-regulation of antigen-specific cellular and humoral immune response	Phase II
MBP8298	Parenteral injection of soluble MBP	Progressive MS	Randomized double blind placebo controlled trial	Benefit in HLA DR2/DR4 patients	Reduced anti-MBP antibodies in CSF	Phase III
TCR vaccination	Trivalent TCR peptide vaccine	RR, SP	Open label	Positive	Induction of TCR specific responses, increased expression of FOXP3	Phase II
Soluble MHC loaded with peptide	Solubilized complex of DR2 with MBP	SP	Double masked, dose escalation	Safe, no effect on clinical activity	No tolerization effect of MBP reactive T cells	–
APL	Altered peptide ligand	RR	Open label MRI controlled / randomized placebo controlled /	Stopped due to exacerbations / hypersensitivity	Activation of MBP specific T cells / induction Th2 response	Phase II

RR: relapsing-remitting MS; SP: secondary progressive MS; MBP: myelin basic protein; TCR: T cell receptor; APL: altered peptide ligand; HLA: human leukocyte antigen; MRI: magnetic resonance imaging; FOXP3: forkhead box 3.